Effect of intraoperative high inspired oxygen fraction on surgical site infection, postoperative nausea and vomiting, and pulmonary function: Systematic review and meta-analysis of randomized controlled trials

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Abstract: BACKGROUND:: Intraoperative high inspired oxygen fraction (FIO2) is thought to reduce the incidence of surgical site infection (SSI) and postoperative nausea and vomiting, and to promote postoperative atelectasis. METHODS:: The authors searched for randomized trials (till September 2012) comparing intraoperative high with normal FIO2 in adults undergoing surgery with general anesthesia and reporting on SSI, nausea or vomiting, or pulmonary outcomes. RESULTS:: The authors included 22 trials (7,001 patients) published in 26 reports. High FIO2 ranged from 80 to 100% (median, 80%); normal FIO2 ranged from 30 to 40% (median, 30%). In nine trials (5,103 patients, most received prophylactic antibiotics), the incidence of SSI decreased from 14.1% with normal FIO2 to 11.4% with high FIO2; risk ratio, 0.77 (95% CI, 0.59-1.00). After colorectal surgery, the incidence of SSI decreased from 19.3 to 15.2%; risk ratio, 0.78 (95% CI, 0.60-1.02). In 11 trials (2,293 patients), the incidence of nausea decreased from 24.8% with normal FIO2 to 19.5% with high FIO2; risk ratio, 0.79 (95% CI, 0.66-0.93). In patients receiving inhalational anesthetics without prophylactic antiemetics, high FIO2 provided a significant protective effect against both nausea and vomiting. Nine trials (3,698 patients) reported on pulmonary outcomes. The risk of atelectasis was not increased with high FIO2. CONCLUSIONS:: Intraoperative high FIO2 further decreases the risk of SSI in surgical patients receiving prophylactic antibiotics, has a weak beneficial effect on nausea, and does not increase the risk of postoperative atelectasis.

DOI: https://doi.org/10.1097/ALN.0b013e31829aaff4

MS # ALN201207048: 5th **Revision**

Effect of Intra-operative High Inspired Oxygen Fraction on Surgical Site Infection, Postoperative Nausea and Vomiting, and Pulmonary Function

Systematic Review and Meta-analysis of Randomized Controlled Trials

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MS Statistics

words abstract: 248

words introduction: 291

words discussion: 1114

Additional Information

Support was provided solely from institutional and/or departmental sources.

Presented at the Euroanaesthesia Meeting, Paris, France, June 9-12, 2012.

Supplementary material is freely accessible on the author's Web site at http://www.hcuge.ch/anesthesie/data.htm.

Abbreviated Title

Benefit and harm of intra-operative high FIO_2.

Acknowledgements

The authors thank Pascal Thibon, M.D., M.Sc., Staff Infection Control Physician and Epidemiologist, Antenne, Régionale de Lutte contre les Infections Nosocomiales de Basse-Normandie, Centre Hospitalier Universitaire de Caen, Caen, France who kindly responded to our inquiries.

Summary Statement

Intra-operative high FIO_2 decreases the risk of surgical site infection in surgical patients receiving prophylactic antibiotics, has a weak beneficial effect on nausea, and does not increase the risk of postoperative atelectasis.

Abstract

BACKGROUND: Intra-operative high inspired oxygen fraction (FIO_2) is thought to reduce the incidence of surgical site infection and postoperative nausea and vomiting, and to promote postoperative atelectasis.

METHODS: We searched for randomized trials (to 09.2012) comparing intra-operative high with normal FIO_2 in adults undergoing surgery under general anesthesia and reporting on surgical site infection, nausea or vomiting, or pulmonary outcomes.

RESULTS: We included 22 trials (7,001 patients) published in 26 reports. High FIO_2 ranged from 80% to 100% (median, 80%); normal FIO_2 ranged from 30% to 40% (median, 30%). In 9 trials (5,103 patients, most received prophylactic antibiotics), the incidence of surgical site infection decreased from 14.1% with normal FIO_2 to 11.4% with high FIO_2; risk ratio 0.77 (95% confidence interval, 0.59 to 1.00). After colorectal surgery, the incidence of surgical site infection decreased from 19.3% to 15.2%; risk ratio 0.78 (95% confidence interval, 0.60 to 1.02). In 11 trials (2,293 patients), the incidence of nausea decreased from 24.8% with normal FIO_2 to 19.5% with high FIO_2; risk ratio 0.79 (95% confidence interval, 0.66 to 0.93). In patients receiving inhalational anesthetics without prophylactic anti-emetics, high FIO_2 provided a significant protective effect against both nausea and vomiting. Nine trials (3,698 patients) reported on pulmonary outcomes. The risk of atelectasis was not increased with high FIO_2.

CONCLUSIONS: Intra-operative high FIO_2 further decreases the risk of surgical site infection in surgical patients receiving prophylactic antibiotics, has a weak beneficial effect on nausea, and does not increase the risk of postoperative atelectasis.

Introduction

It has been claimed that patients undergoing surgery under general anesthesia were benefiting from a higher than normal inspired oxygen fraction (FIO_2).[1,2] Some authors have suggested that a high FIO_2 was a simple, inexpensive, and low-risk intervention and that the broader use of this technique should be encouraged in patients undergoing major abdominal procedures.[3] Randomized trials have reported on a reduced risk of surgical site infection (SSI) in patients who were ventilated with 80% FIO_2 during surgery.[4,5] It was also shown that patients who were ventilated with high FIO_2 intra-operatively had a reduced incidence of postoperative nausea and vomiting (PONV).[6,7]

Other authors were more cautious.[8,9] Skepticism has been partly related to the fact that high FIO_2 may have deleterious effects in the airways. One hundred percent oxygen at induction or at the end of general anesthesia has been suggested to promote atelectasis over a few minutes,[10-12] and to cause alteration in gas exchange.[13]

Both SSI and PONV remain a crucial topic for anesthetists and surgeons, as they represent a significant clinical and economical burden; SSI may lead to prolonged length of stay and increased hospital costs,[14-16] while PONV symptoms are among the most frequent adverse effects of anesthesia and surgery and they are also associated with incremental costs.[17-19] Meta-analyses of clinical trials addressing the potential benefit of high FIO_2 in surgical patients have reported on conflicting results.[20-26] A number of further relevant clinical trials studying these issues have been published recently.[27-30] The aim of our study was to update previously published meta-analyses, and to provide a comprehensive quantitative summary of the most important, potentially beneficial (decrease in the risk of SSI or PONV) and

harmful (increase in the risk of pulmonary complications) effects of intra-operative high inspired FIO_2 in surgical patients.

Materials and Methods

We followed the PRISMA guidelines for the reporting of meta-analyses of randomized controlled trials.[31]

Eligibility Criteria

We searched for published full reports of randomized comparisons of intra-operative high FIO_2 (experimental intervention) versus normal (i.e. "low") FIO_2 (control intervention). A high FIO_2 was defined as a FIO_2 ≥50% and a normal FIO_2 as a FIO_2 <50%.

In trials with a limited high-to-normal FIO_2 ratio, the difference in oxygen regimens may be too small and consequently the high FIO_2 regimen may not have the scope to show efficacy. Also, such trials may produce positive results by random chance. Consequently, there was an arbitrary *pre hoc* decision to include only studies where the normal FIO_2 value was less than, or equal to, half of the high FIO_2 value.

We considered studies that were performed in adult patients (≥ 18 years) undergoing any surgical procedure under general anesthesia and that reported on at least one of three outcomes: (1) SSI; (2) PONV; (3) intra- or postoperative pulmonary outcomes.

Data from animal studies or abstracts were not considered. Reports of patients undergoing surgery with regional anesthesia, patients undergoing one-lung surgery, or patients receiving high FIO_2 in other settings than general anesthesia for surgery as, for instance, patients ventilated in the intensive care or in the pre-hospital setting, were excluded. Studies where supplemental oxygen was administered only postoperatively, or for a restricted time during anesthesia (for instance, at induction or during a short period before extubation), were not considered**.**

Information Sources

We performed a variety of high sensitivity and low specificity searches for relevant reports in the Medline, Embase, and Central databases. Key words ("oxygen", "supplemental", "anesthesia") were combined using the Boolean meanings of "and" and "or". The last electronic search was in September 2012. Bibliographies of retrieved articles were searched for additional references. We applied no restriction on language.

Study Selection

Retrieved articles were reviewed for inclusion by one author (FH) and criteria for inclusion were independently checked by another author (CL). Queries were resolved through discussion with a third author (MRT).

Risk of Biases in Individual Studies

Quality of data reporting was assessed by one author (FH) and was independently checked by another (CL), using a modified 4-items, 7-points Oxford scale taking into account method of randomization, concealment of treatment allocation, degree of blinding, and reporting of drop-outs, as previously described.[32] Consensus was reached by discussion with a third author (MRT).

Since potential confounding factors (for instance, carrier gas or fluid regimen) may directly affect the occurrence of SSI, regardless of the FIO_2,[1,33,34] we retrieved such information from each study. For the analysis of SSI data, nitrous oxide was not regarded as a potential confounding factor.[35] However, for the analyses of PONV data, we excluded data from studies that were using nitrous oxide as a carrier gas, since nitrous oxide has emetogenic properties.[36]

Data Extraction Process

One author (FH) extracted all relevant information from original reports. Another author (CL) independently checked all extracted data. Discrepancies were resolved by discussion with a third author (MRT).

Data items

Definitions of SSI were taken as reported in the original reports.

Three distinct PONV outcomes were analyzed:[37] nausea, vomiting (including retching), and a composite endpoint (i.e. nausea and/or vomiting/retching). Cumulative incidences of these outcomes were extracted for two time periods, an early period (0 to 6 hours), and a late period (0 to 24 hours).

Pulmonary complications were defined as any adverse event occurring intra- or postoperatively and affecting the lower respiratory tract and/or interfering with normal test values related to lung integrity (blood gases, spirometry, chest imagery, arterial oxygen saturation measure through pulse oximetry, postoperative oxygen requirements).

Synthesis of Results

For dichotomous data, we calculated risk ratios (RR) with 95% confidence intervals (CI). When the 95% CI around the RR point estimate did not include 1, the difference between experimental and control group was considered statistically significant.

For continuous data, weighted mean differences with 95% CI were calculated.

We performed formal heterogeneity testing. When the data were homogenous (P≥0.1), we used a fixed effect model to combine data from independent trials. When the data were

heterogeneous, we searched for sources of heterogeneity. For example, if one study showed results that were completely out of range of the others, we searched for likely reasons explaining the difference and performed a sensitivity analysis excluding that study, when deemed appropriate. When no source could be identified that explained the heterogeneity, we combined the data using a random effects model. Sources of heterogeneity to be sought were not pre-specified.

Analyses were performed using STATA 11 (Version 11, STATA Corp, College Station, TX), RevMan (Computer Program, version 5.1.6, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, Denmark), and Microsoft® Excel® 12.2.3. for Mac (Microsoft Corporation, Redmond, WA).

Results

Study Selection

We retrieved 204 articles (FIGURE 1). Of 45 potentially relevant randomized trials, 19 were excluded after more thorough examination. In 4, the inspired oxygen fraction in control patients was >50%.[38-41] Data of 6 studies could not be extracted for meta-analysis: 4 reported measures of associations[42-45] and 2 provided results in graphical format only.[46,47] Three included data from children.[48-50] In 3 trials, the oxygen fraction administrated in the control group was more than half of that administrated in the experimental group; 2 of those compared 50% with 30%,[51,52] and one compared 60% with 45%.[53] One trial was using nitrous oxide as a carrier gas and reported on PONV outcomes only.[54] Finally, 2 studies were recently retracted due to ethical concerns.[‡§]

We eventually included data from 22 randomized trials (7,001 patients) that were reported in 26 articles.[4-7,27-30,55-72] Seven reports with additional data from 900 patients have not been considered for any previously published meta-analyses.[27-30,61,69,70] Two articles reporting on pulmonary outcomes[56] and PONV,[7] respectively, were subgroup analyses of a multicenter study that reported on SSI.[5] Results of another multicenter study reporting on SSI and pulmonary outcomes[63] were reported in 2 further articles; one concentrated on pulmonary outcomes in obese patients,[70] the other on pulmonary outcomes in patients scheduled for laparotomy for ovarian cancer.[69]

[‡]Ochmann C, Tuschy B, Beschmann R, Hamm F, Rohm KD, Piper SN: Supplemental oxygen reduces serotonin levels in plasma and platelets during colorectal surgery and reduces postoperative nausea and vomiting. Eur J Anaesthesiol 2010; 27: 1036-43

[§]Fujii Y, Itakura M: Supplemental intraoperative oxygen prevents postoperative nausea and vomiting inpatients undergoing gynecological laparoscopic surgery. Anesthesia and Resuscitation 2008; 44: 47-50

Study Characteristics

Included reports were published between 2000 and 2012 (tables 1-3). The median quality score was 5.5 (range, 2 to 7). In experimental groups, intra-operative FIO_2 ranged from 80% to 100% (median, 80%), in controls ranged from 30% to 40% (median, 30%).

Synthesis of Results

Surgical Site Infection

Nine studies (5,103 patients) reported on the incidence of SSI (table 1).[4,5,28,30,58,62-64,66] Six studies considered SSI as an infection occurring within 14 days postoperatively, and 2 within 30 days;[30,62] one trial did not mention the duration of follow-up.[28] Seven studies used a standardized method for SSI assessment: 3 considered the ASEPSIS scoring system,[4,5,58] 2 used the definition of the Centers for Disease Control and Prevention,[30,63] and 2 considered a prospectively determined scoring system.[28,66] In all trials except one,[30] 90 to 100% of patients received prophylactic antibiotics.

Surgeries were colorectal, appendectomy, abdominal, and gynecologic. Two trials reported on abdominal and non-abdominal procedures.[30,64] The baseline risk of SSI, i.e. the incidence of SSI in patients receiving normal FIO_2, ranged from 7%[30] to 27%.[28] When data were combined, there was an average incidence of 14.1% with normal FIO_2 and of 11.4% with high FIO_2; RR 0.77 (95%CI, 0.59 to 1.00) (FIGURE 2A). Because data were heterogeneous (P_{hetero}=0.03), we used a random effects model.

Since it has been argued that patients undergoing colorectal surgery may particularly profit from a high FIO_2 regimen,[24,26] we performed a subgroup analysis including all patients undergoing colorectal surgery. Four trials were performed exclusively in patients undergoing

colorectal surgery,[4,5,28,62] and from 4, data from patients undergoing colorectal surgery could be extracted.[30,63,64,66] When all colorectal surgery data were combined (n=1,977), there was an average incidence of SSI of 19.3% with normal FIO_2 and of 15.2% with high FIO_2; RR 0.78 (95%CI, 0.60 to 1.02) (FIGURE 2B). The data were homogenous (P_{hetero}=0.19). We additionally performed a meta-analysis using a fixed effect model; the RR was 0.80 (95% CI, 0.66 to 0.97).

Postoperative Nausea and Vomiting

Eleven trials (2,293 patients) reported dichotomous data on presence or absence of nausea or vomiting (table 2).[6,7,27,29,30,57,59,65,67,68,71]

When combining all data, only prevention of late nausea showed statistical significance in favor of high FIO_2 (FIGURE 3A). With normal FIO_2, the average incidence of late nausea was 24.8%, with high FIO_2 was 19.5%; RR 0.79 (95%CI, 0.66 to 0.93).

Since propofol and prophylactic anti-emetics reduce the underlying risk of PONV, we performed a sensitivity analysis including exclusively data from patients who received an inhalational anesthetic without prophylactic anti-emetics.[6,7,27,29,57,59,67,68] As expected, incidences of PONV outcomes in patients receiving normal FIO_2 were increased (FIGURE 3B). With normal FIO_2, the average incidence of late nausea was 33.7%, with high FIO_2 was 29.3%; RR 0.75 (95%CI, 0.62 to 0.90). With normal FIO_2, the average incidence of late vomiting was 26.2%, with high FIO_2 was 19.2%; RR 0.72 (95%CI, 0.56 to 0.92). When analyzing the composite endpoint PONV, no statistical significance was reached.

Pulmonary Outcomes

Nine trials (3,698 patients) reported on pulmonary outcomes (table 3).[55,56,60,61,63,64,69,70,72] Six articles reported on atelectasis using chest radiographs and/or thoracic computed

tomography-scans for diagnosis (table 4); however, 2 of those[69,70] were subgroup analyses reporting on the same outcomes as the original larger study.[63] Thus, data from 4 trials, 2 small[56,60] and 2 large,[63,64] could be combined (FIGURE 4). The average incidence of atelectasis with high FIO_2 was 8.3%, with normal FIO_2 was 10.6%; RR 0.93 (95%CI, 0.59 to 1.46).

Three small trials reported on peri-operative blood gas analyses (table 4).[55,60,69] In one,[55] there was evidence of a statistically significant worsening of the intra-operative PaO_2/FIO_2 ratio in patients receiving 100% FIO_2 (use of positive end-expiratory pressure and postoperative PaO_2/FIO_2 ratio were not reported). The 2 other studies failed to show any detrimental effect on the postoperative PaO_2/FIO_2 ratio with supplemental oxygen,[60,69] despite the use of 100% oxygen and no positive end-expiratory pressure in one trial.[60]

Three small studies reported on lung function (table 4).[56,69,72] In 2, spirometry values were not different in patients receiving high or normal FIO_2.[56,69] The third, including 142 moderately obese patients, reported on a variety of postoperative spirometric values that were significantly worsened with high oxygen fraction.[72] Specifically, there was a linear decrease in postoperative lung function with increasing body mass index in the high-oxygen group.

Two studies reported on postoperative SpO_2 values.[69,72] Both failed to show a significant decrease in the 24h-postoperative SpO_2 in patients exposed to high FIO_2.

Finally, one trial showed no difference in postoperative oxygen requirements among patients ventilated with a high or normal FIO_2.[61]

Discussion

We performed a systematic review and meta-analysis of clinical trials testing the role of high inspired oxygen fraction in patients undergoing surgery under general anesthesia. We studied outcomes that are relevant in this context, i.e. SSI, PONV, and pulmonary complications. We analyzed data from 22 randomized trials (including 7,001 patients) that were reported in 26 articles.

When combining data of all eligible patients, regardless of the type of surgery, the risk of SSI decreased by 23% with high FIO_2 (RR 0.77), and the difference was borderline statistically significant. When selecting patients undergoing colorectal surgery, the RR point estimate was similar, and, depending on the statistical model that was used, the 95% confidence interval included (random effects model) or excluded (fixed effect model) equality. Previous meta-analyses have yielded conflicting results on the potential benefit of high FIO_2 on SSI. Three reported on a significant reduction in the incidence of SSI.[20,22,24] A fourth analysis, similar to ours, reported on a statistically significant result in favor of high FIO_2 when a fixed effect model was used but failed to show any benefit with a random effects model.[21] Finally, a fifth analysis reported on a protective effect with high FIO_2 in patients undergoing colorectal surgery only, but not in patients undergoing other abdominal surgeries.[26] Many authors have considered that subgroup as the most likely to profit from a high FIO_2.[24,26] The question then is, whether this benefit is of clinical relevance. Although the degree of anti-infective efficacy of high FIO_2 seems weak and perhaps disappointing, it appears to be similar to conventional antibiotic prophylaxis in many surgical settings.[73] Also, as most patients in these trials had received prophylactic antibiotics, we may conclude on the efficacy of high FIO_2 as a supplemental anti-infection strategy only; the efficacy of high FIO_2 alone remains

unclear and would be difficult to test from an ethical perspective, since the administration of prophylactic antibiotics is widely considered as standard of care. In some trials, the incidence of SSI in controls was very low and in others it was above 20%, despite prophylactic antibiotics. High FIO_2 appeared to be effective independent of the baseline risk of infection (FIGURE 2A).

The potentially beneficial effect of high FIO_2 on the incidence of PONV has been contentious too. In 2007, an international consensus panel did not recommend supplemental oxygen for the prevention of PONV.[74] In 2008, 2 meta-analyses were addressing the potential benefit of high FIO_2 on PONV; one concluded that supplemental oxygen reduced the incidence of postoperative vomiting only,[25] the other was unable to identify any beneficial effect of high FIO_2.[23] In our analysis, there was some evidence that high FIO_2 decreased the incidence of both nausea and vomiting in patients receiving an inhalational anesthetic and no prophylactic anti-emetics. The baseline risk (i.e. the incidence of PONV in controls) was increased in this context, and this may explain why high FIO_2 had more scope to show antiemetic efficacy. However, absolute risk reductions suggested that about 15 patients needed to receive high FIO_2 for one not to be nauseous or to vomit who would have done so had they received normal FIO_2. This degree of prophylactic antiemetic efficacy is weak, as numbers-needed-to-treat of 3 to 5 (absolute risk reduction, 20 to 30%) may be expected from an effective pharmacological antiemetic intervention in the surgical setting.[74] Also, when analyzing the composite endpoint, PONV, no benefit was evident.

Nine trials reported on a large variety of pulmonary outcomes, including atelectasis, blood gases, lung spirometry or postoperative SpO_2. Results were difficult to compare as outcome measures differed among studies. Dichotomous data on presence or absence of atelectasis

could be combined from 2 small and 2 large trials. The result was clearly negative. Two studies reported on postoperative PaO_2/FIO_2 ratio. Both failed to show any detrimental effect of high FIO_2 on postoperative gas exchange, despite using ventilation settings known to acutely worsen pulmonary atelectasis[11] (i.e. administration of 100% FIO_2 without positive end-expiratory pressure) in one trial. Additionally, in 3 studies reporting on surrogate outcomes, there was no evidence of pulmonary harm when using a high FIO_2 regimen. Only one trial, conducted in moderately obese patients, reported on a detrimental effect of high FIO_2 on spirometric values postoperatively.

Our aim was to combine data from well-controlled trials that had the scope to show beneficial or harmful effects of high FIO_2, if there were any. Our study differs twofold from previously published similar meta-analyses.[20-26] Firstly, none of the previously published meta-analyses attempted to provide a complete picture of the potentially beneficial (SSI, PONV) and harmful (pulmonary complications) effects of high FIO_2. Secondly, our selection criteria were stricter. For instance, we excluded studies where oxygen was delivered via a facemask in awake patients undergoing regional anesthesia,[75-79] or where supplemental oxygen was provided to patients in the postoperative period only.[80-82] Finally, to ensure that the trials had the scope of showing an effect with high FIO_2, we arbitrarily defined that, for eligibility, the value of the normal FIO_2 had to be less than, or equal to, half of the high FIO_2 value.

Included trials were performed in patients undergoing different surgical procedure, with a variety of anesthetic regimens. Ideally, we would adjust these analyses for potential confounding factors; in practice, this was not feasible as the number of analyzed trials was limited. Critical analysis of all included trials suggested that they did not differ that much

regarding potential confounders (table 1-3). Also, a certain degree of clinical heterogeneity ensures wide applicability, or external validity, of the results of these analyses. However, since all trials were performed in adults only, the results may not be applicable to children. We did not include data from children,[48-50] as there is an argument, at least when testing the efficacy of an antiemetic intervention in the surgical setting, to distinguish between children and adults.[83] Also, since trials reporting on SSI included mainly patients undergoing abdominal surgery, extrapolation of our results to other types of surgery remains speculative. Concerning antibiotic prophylaxis it has been argued that its efficacy in reducing the risk of wound infection may be assumed for all types of surgery, even ones where no clinical trial data exist.[73]

In conclusion, intraoperative high FIO_2 may be regarded as a supplemental strategy to further decrease the risk of SSI in patients receiving prophylactic antibiotics. Indirect comparison suggests that the degree of efficacy is similar to antibiotic prophylaxis in many surgical settings. However, the efficacy of high FIO_2 *per se*, and in the absence of antibiotic prophylaxis, remains unknown. High FIO_2 reduces the risk of PONV to some extent, although mainly in patients undergoing inhalation anesthetics and without prophylactic anti-emetics. Finally, intra-operative high FIO_2 does not increase the risk of postoperative atelectasis.

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